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Smoking and Drug Interactions

Virginia Ernster, in her excellent editorial in the September issue, summarized the increased risk of various health endpoints—such as cancer, heart attack, stroke, and emphysema—faced by smokers.[1] Another endpoint often neglected is that of altered drug response. Tobacco smoke is a potent inducer of hepatic enzymes.[2,3] As a result, the metabolism of several medications is enhanced, which often leads to decreased efficacy. For example, smokers may require from one third to twice the dose of theophylline needed by nonsmokers.[3–5] The response to certain pain medication, such as propoxyphene, is diminished in smokers.[6] And the interaction between smoking and oral contraceptives is a complex and deadly one; women more than 35 years old who smoke more than 15 cigarettes a day are clearly at increased risk of myocardial infarction.[7]

The alteration of drug response in smokers must be added to the overwhelming weight of evidence against smoking. □

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Access to Comprehensive Health Services Is Fundamental

I am writing to commend the editors and contributors for an exceptional March 1993 issue of the Journal and to comment on the dearth of primary care physicians graduating from medical training in the United States and the problems of the British Health Service.

Susser[1] points out that, according to health outcome measures in Britain, the lower socioeconomic strata have failed to close the health gap between themselves and higher socioeconomic groups despite full access to care. He attributes this failure to a decline in the power and effectiveness of the public health authorities. I surmise that Susser's point is to warn public health practitioners that upcoming US reforms are likely to fail if they do not also strengthen the role and authority of the public health sector (i.e., health promotion, health education, populationwide disease prevention, system evaluation, and health standards enforcement).

I do subscribe to this view. However, as Susser's first general requirement of health care as a right is access, health care problems in the United States today are more fundamentally the result of a discriminatory health care system. This, coupled with the failure to strengthen the training in and fair distribution of primary care disciplines, suggest that—in the face of uncontrolled cost—more than simple structural change will be needed.

Rosenblatt et al.[2] and Geiger[3] point out that the National Institutes of Health research funding for medical schools totally overwhelms the small amount of funds available for primary care program development. This resource allocation problem has distorted the policy programs of our schools of public health, as well as of our medical schools, because policy and program development have been driven more by funding than by public need.

Most readers will agree that health outcome measures may not equilibrate without major public health authority and financing. But the problems of the health care system in the United States cannot be fixed by public health advocacy separately since equal access to health services is a more fundamental prerequisite. Providing sufficient primary care practitioners (who ought to be well trained in prevention and public health) to meet this need is required. □

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Note. The views expressed here are solely the author's.

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Vitamin Supplement Use and Mortality

1. Study That Found No Relationship Is Challenged

In concluding that vitamin supplements have no relationship to mortality, Kim et al.[1] overlooked my findings based on the same First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS) database. My analysis shows that there is a weak relationship in the cohort as a whole and a stronger one in a portion of the cohort. To demonstrate this relationship, I present here results based on a follow-up of the NHEFS cohort through 1987,[3] the same follow-up period used by Kim et al. Of the 11 348 persons in the NHEFS cohort, 474 persons were lost to follow-up after enrollment and a total of 4333 men and 6541 women were followed.

First, note that the corrected Table 1 of Kim et al. (shown here as Table 2 in Kim's response) shows lower age-specific

TABLE 1—Standardized Mortality Ratios (SMRs) for All Causes of Death during the Years 1971 through 1987 as a Function of Regular Vitamin Supplement Use during the Years 1971 through 1974: NHEFS Cohort

	Regular Supplement Users		Nonusers	
	No. of Observed Deaths	SMR (95% CI)	No. of Observed Deaths	SMR (95% CI)
Total cohort				
Men	308	0.89 (0.80, 1.00)	1161	1.03 (0.97, 1.09)
Women	335	0.95 (0.85, 1.06)	807	1.03 (0.96, 1.11)
Both sexes	643	0.92 (0.85, 1.00)	1968	1.03 (0.99, 1.08)
Users of ≥50 mg/day vitamin C				
Men	165	0.74 (0.63, 0.86)	592	0.95 (0.88, 1.03)
Women	214	0.92 (0.80, 1.05)	447	1.04 (0.95, 1.14)
Both sexes	379	0.83 (0.75, 0.92)	1039	0.99 (0.93, 1.05)

Note. Comparisons are made relative to contemporaneous US whites (with SMR = 1.00). NHEFS = First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study; CI = confidence interval.

death rates in four of the five age groups and a lower age-adjusted death rate for regular supplement users than for nonusers, although the differences are not statistically significant. However, the differences are more pronounced when expressed in terms of the standardized mortality ratio, which is the ratio of observed deaths to expected deaths based on contemporaneous death rates for US Whites.[4] As I show in Table 1 here, the standardized mortality ratio for regular supplement users is lower than that of nonusers by 14% for men, 8% for women, and 11% for both sexes combined.

Furthermore, among those consuming at least 50 mg of dietary vitamin C, the standardized mortality ratio for regular supplement users is lower than that of nonusers by 22% for men, 12% for women, and 16% for both sexes combined. These differences are statistically significant for men and for both sexes combined. The subgroup of those consuming at least 50 mg of dietary vitamin C is roughly the same as the Kim et al. subgroup with no "deficient" nutrients. Kim et al.'s corrected table (Table 2) shows the age-adjusted death rates of regular supplement users in this subgroup to be 14% lower than those of nonusers for both men and women, differences that appear to be statistically significant.

Cox proportional hazards linear models have been applied to the NHEFS cohort to determine how the differences in Table 1 are affected by the 10 confounding variables used in my previous analyses.[2,3] For men, the relative risk for regular supplement users compared with nonusers is significantly less than 1.0 before adjustment, but not after adjustment, when vitamin supplement use is the independent variable. However, the relative risks before adjustment (0.66, 95% confidence interval [CI] = 0.57, 0.77) and after adjustment (0.80, 95% CI = 0.67, 0.96) are both significantly less than 1.0 when my three-level vitamin C index is the independent variable.[2,3] For women, the relative risk is not significantly different from 1.0 before or after adjustment for vitamin supplement use or the vitamin C index.

In summary, there are several results from the NHEFS that are contrary to Kim et al.'s conclusion that there is no evidence of reduced mortality among vitamin and mineral supplement users in this study. Further research is necessary to comprehensively measure the health effects of vitamin supplements. □

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2. Kim et al. Respond

Enstrom et al. reported on 10-year mortality relative to intake of vitamin C from both diet and supplements,[1] whereas we reported on 17-year mortality relative to the use of any type of vitamin or mineral supplements. The exposure categories created by Enstrom et al. were defined as a combination of vitamin C from supplements and dietary vitamin C intake, based on subjects' 24-hour recall. The new analysis presented in Dr Enstrom's letter[3] is an improvement over Enstrom et al.'s previous analysis because exposure categories are defined only by supplement use. However, interpretation of the associations he reports between supplement use and mortality is still difficult for two reasons: contrasts in standardized mortality ratios from two groups that differ in age structure (as do supplement users and nonusers) can be misleading,[4(pp45–49)] and the standardized mortality ratio adjustment is only for age. Many characteristics of vitamin supplement users are related to lower mortality, including White race, higher educational level, lower weight, and better diet.

While we were corresponding with Dr Enstrom, it was discovered that the rates presented in Table 1 of our paper had been age-adjusted separately for users and nonusers of supplements, contrary to the method described in the text. Because our analysis of mortality differences associated with supplements was based on proportional hazards analysis, none of our conclusions were affected by the age-adjustment procedure reflected in the table. Nonetheless, because the rates reported in our original Table 1 could be misused by readers, mortality rates adjusted to a common reference population are presented here as Table 2. Table 2 also shows relative risks of mortality for regular supplement users, adjusted only for age and race and adjusted for various other cofactors. These details are included so the association in the particular